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<b>(21) International Application Number:</b> PCT/GB99/03774 <b>(22) International Filing Date:</b> 12 November 1999 (12.11.99)  <b>(30) Priority Data:</b> 60/108,121 12 November 1998 (12.11.98) US 9900824.5 14 January 1999 (14.01.99) GB  <b>(71) Applicant (for all designated States except US):</b> NYCOMED AMERSHAM PLC [GB/GB]; Amersham Laboratories, White Lion Road, Amersham, Buckinghamshire HP7 9LL (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MCINTIRE, Gregory, Lynn [US/US]; Nycomed Amersham Imaging, 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087-8630 (US). BACON, Edward, Richard [US/US]; Nycomed Amersham Imaging, 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087-8630 (US). SNOW, Robert, Allen [CA/US]; Nycomed Amersham Imaging, 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087-8630 (US). GUSTOW, Evan [US/US]; Nycomed Amersham Imaging, 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087-8630 (US).		<b>(74) Agent:</b> FRANK B. DEHN & CO.; 179 Queen Victoria Street, London EC4V 4EL (GB).  <b>(81) Designated States:</b> AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title: PRODUCTS AND METHODS</b>		
<b>(57) Abstract</b> <p>Radioactive sources suitable for use in brachytherapy comprising one or more insoluble salts, wherein the insoluble salt contains, or the insoluble salts together contain, at least two different radioisotopes. Preferred radioisotopes are <sup>103</sup>Pd and <sup>125</sup>I and preferred insoluble salts include <sup>103</sup>Pd(<sup>125</sup>I<sub>2</sub>), <sup>103</sup>Pd<sup>35</sup>S, <sup>89</sup>Sr<sup>32</sup>PO<sub>4</sub> and <sup>89</sup>Sr<sup>35</sup>SO<sub>4</sub>.</p>		

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Products and Methods

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This invention relates to radiotherapy. More particularly, it relates to radioisotopes and radioactive sources for use in brachytherapy.

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Brachytherapy is a general term covering medical treatment which involves the temporary or permanent implantation or insertion of a radioactive source into the body of a patient. The radioactive source is thereby  
15 located close to the area of the body which is being treated. This has the advantage that a high dose of radiation may be delivered to the treatment site with relatively low dosages of radiation to surrounding healthy tissue.

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Brachytherapy has been proposed for use in the treatment of a variety of conditions, including arthritis and cancer, for example breast, brain, liver and ovarian cancer and especially prostate cancer in men (see for  
25 example J.C. Blasko et al., *The Urological Clinics of North America*, 23, 633-650 (1996), and H. Ragde et al., *Cancer*, 80, 442-453 (1997)). Prostate cancer is the most common form of malignancy in men in the USA, with more than 44,000 deaths in 1995 alone. Treatment may involve  
30 the temporary implantation of a radioactive source for a calculated period, followed by its removal. Alternatively, the radioactive source may be permanently implanted in the patient and left to decay to an inert state over a predictable time. The use of temporary or  
35 permanent implantation depends on the isotope selected and the duration and intensity of treatment required.

Permanent implants for prostate treatment comprise radioisotopes with relatively short half lives and lower energies relative to temporary sources. Examples of permanently implantable sources include iodine-125 or palladium-103 as the radioisotope. The radioisotope is generally encapsulated in a titanium casing to form a "seed" which is then implanted. Temporary implants for the treatment of prostate cancer may involve iridium-192 as the radioisotope.

Recently, brachytherapy has also been proposed for the treatment of restenosis (for reviews see R. Waksman, *Vascular Radiotherapy Monitor*, 1998, 1, 10-18, and *MedPro Month*, January 1998, pages 26-32). Restenosis is a renarrowing of the blood vessels after initial treatment of coronary artery disease.

Coronary artery disease is a condition resulting from the narrowing or blockage of the coronary arteries, known as stenosis, which can be due to many factors including the formation of atherosclerotic plaques within the arteries. Such blockages or narrowing may be treated by mechanical removal of the plaque or by insertion of stents to hold the artery open. One of the most common forms of treatment is percutaneous transluminal coronary angioplasty (PTCA) - also known as balloon angioplasty. At present, over half a million PTCA procedures are performed annually in the USA alone. In PTCA, a catheter having an inflatable balloon at its distal end is inserted into the coronary artery and positioned at the site of the blockage or narrowing. The balloon is then inflated which leads to flattening of the plaque against the artery wall and stretching of the artery wall, resulting in enlargement of the intraluminal passage way and hence increased blood flow.

PTCA has a high initial success rate but 30-50% of patients present themselves with stenotic recurrence of the disease, i.e. restenosis, within 6 months. One treatment for restenosis which has been proposed is the use of intraluminal radiation therapy. Various isotopes including iridium-192, strontium-90, yttrium-90, phosphorous-32, rhenium-186 and rhenium-188 have been proposed for use in treating restenosis.

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Conventional radioactive sources for use in brachytherapy include so-called seeds, which are sealed containers, for example of titanium, containing the radioisotope within a sealed chamber but permitting radiation to exit through the container/chamber walls. Such seeds are only suitable for use with radioisotopes which emit radiation which can penetrate the chamber/container walls. Therefore, such seeds are generally used with radioisotopes which emit  $\gamma$ -radiation or low-energy X-rays, rather than with  $\beta$ -emitting radioisotopes.

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Solutions of radioactive isotopes inside a catheter balloon have also been proposed for use in the treatment of restenosis (US 5616114). However, the use of radioactive liquids increases the risks involved with the procedure due to the possibility of leakage of the radioactive material either inside the patient or when the catheter is being transported, stored or set up.

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Given the increasing importance of brachytherapy, there is a need for a wide range of suitable radiation sources to be readily available, to allow flexibility in matching a source to the required treatment. Such sources should preferably limit the risk of exposure of healthy tissue in the patient to radiation if, for example, the

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radioisotope is exposed directly to body fluids either accidentally or when in use.

WO97/49335 proposes insoluble radioactive  
5 pyrophosphate salts for use in brachytherapy. There is a  
limited range of suitable insoluble pyrophosphate salts  
available. Phosphorus-32 is a  $\beta$ -emitter and hence salts  
comprising  $^{32}\text{P}$  are not suitable for use in conventional  
sealed sources, for example metal seeds, where the wall of  
10 the container will absorb most of the radiation emitted.

Radioactive seeds comprising a coating of silver  
iodide on a silver wire are known (US-A 4323055). Such  
seeds are formed by chloriding or bromiding the silver to  
15 form a layer of silver chloride or bromide, and then  
replacing the chloride or bromide with radioactive iodide  
ions by ion exchange.

We now believe that significant advantages attach to  
20 the use of radiation sources comprising insoluble salts of  
radioactive ions in brachytherapy. Such salts are to be  
preferred for use in brachytherapy as they will not  
generally solubilize in blood or other bodily fluids and  
therefore the risk of the release of such salts into the  
25 circulation in the body is reduced. Accidental exposure  
of patients or medical staff to undesirable radiation will  
therefore be less likely. Radioactive sources comprising  
insoluble salts are also generally safer and easier to  
manufacture.

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It would also be advantageous if radioactive sources  
for use in brachytherapy comprising two or more different  
radioisotopes were readily available, as this would allow  
use of sources emitting more than one type of radiation  
35 and/or radiation of different energies, tailored if  
desired to the particular treatment required.

US-A 3663685 discloses radioactive materials for use in brachytherapy which comprise a water-insoluble carrier for radioisotopic ions dispersed in a water-insoluble vehicle. The radioisotope ion may form part of the carrier, for example as the anion or cation of a salt. However there is no mention that more than one radioisotope could be used in the radioactive materials.

10 US-A 5674177 discloses vascular implants including a first nuclide species which has a half life in the range of 7 hours to 7 days and a second nuclide species which has a half life of more than 100 days. The nuclide species are formed by suitable irradiation of a metal alloy and the first nuclide species preferably decays into the second nuclide species. There is no suggestion that the nuclides be comprised in one or more insoluble salts.

20 According to one aspect of the invention there is therefore provided a radioactive source for use in brachytherapy, preferably a sealed source, comprising one or more insoluble salts wherein the insoluble salt(s) together contain at least two different radioisotopes with the proviso that when the source comprises a single insoluble salt then said salt is not a pyrophosphate salt.

The radioactive sources of the invention may also comprise a suitable non-radioactive support for the insoluble salt(s). Suitable support materials include plastics, graphite, zeolites, ceramics, glass, metals, polymer matrices, ion-exchange resins or other, preferably porous, materials. Preferably, such support materials are inert and biocompatible, and will not react with the insoluble salt(s) but merely provide a surface onto which the salt(s) may be immobilised. The support material may be in the form of a bead, wire or rod. The wires or rods

be in the form of a bead, wire or rod. The wires or rods will preferably be X-ray dense e.g. of silver, tungsten, gold or lead.

- 5           The radioactive sources of the invention may also comprise a hollow sealed container encapsulating the insoluble salt(s) either with or without a support. Such containers should be biocompatible. Titanium or stainless steel are suitable materials for such containers, or some  
10 other material which is corrosion resistant, compatible with body fluids and non-toxic, and which does not unduly absorb the radiation emitted from the radioisotope(s). Titanium is a preferred material for the container.
- 15           While conventional seeds use a titanium container welded at both ends, it is not essential that this be the case in the present invention. For the majority of  $\beta$ -emitting radionuclides to be effective in brachytherapy when in a sealed container (i.e. as a sealed source or  
20 device), the container should not block the therapeutical  $\beta$ -particle emissions. Such containers could for example comprise titanium seeds with a thinner wall thickness, other metals with cross-sections which minimise  $\beta$ -particle capture, or polymeric containers which are not  
25 biodegradable within the lifetime of the radionuclide. Any of the supports or carriers mentioned above could also comprise sealed sources by overcoating with a lacquer or varnish that would be tolerable in vivo, yet would allow  $\beta$ -radiation to interact with the desired tissues. Under  
30 such particular circumstances, i.e. when containers are employed which are sufficiently  $\beta$ -particle transparent, the use of pyrophosphates may fall within the scope of the present invention.
- 35           Particles of the insoluble salt(s) may be incorporated within a sealed source, such as a polymer



matrix, glass, or a plastic and/or ceramic composite, or a contained source such as a matrix or part of a matrix or the centre of a matrix in which the salt(s) are enclosed within a container that is not necessarily sealed. If the  
5 salt(s) are enclosed within a polymer matrix, this may subsequently be plated.

Preferably, the support and/or the container are formed of an X-ray dense material, such that the sources  
10 may be more readily located by X-ray imaging techniques during or following implantation or insertion into a patient.

The source should be of a size and dimension suitable  
15 for its intended use. Seeds for use in the treatment of prostate cancer are, for example, typically substantially cylindrical in shape and approximately 4.5mm long with a diameter approximately 0.8mm and are of such a shape that they may be delivered to the treatment site using a  
20 hypodermic needle. For use in the treatment of restenosis, a source should be of suitable dimensions to be inserted inside a coronary artery, for example with a length of 10mm and a diameter of 1mm, preferably a length of 5mm and a diameter of 0.8mm and most preferably with a  
25 length of 3mm and a diameter of 0.6mm.

Preferred insoluble salts are salts comprising one or more of  $^{125}\text{I}$ ,  $^{103}\text{Pd}$ ,  $^{89}\text{Sr}$ ,  $^{35}\text{S}$  and  $^{32}\text{P}$ , for example strontium phosphate, carbonate or sulphate and palladium oxide,  
30 hydroxides, iodide or bromide.

By way of example, some radionuclides of interest for inclusion in the sources of the invention, especially sealed sources, include the following:  
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Radionuclide	half life (days)	emission type	energy (MeV)	pathlength (microns)
Phosphorus				
32	14.282	beta	1.71	2.7
33	25.3	beta	0.25	
Iodine				
123	0.52	gamma	0.159	0.42
		X-ray	Te-x	
125	60.14	gamma	0.035	
		X-ray	Te-x	
131	8.0	beta	0.607, 0.336	
		gamma	0.283, 0.364, 0.637, 0.723	
		X-ray	Xe-x	
Palladium				
103	16.97	gamma	0.270, 0.296	3.9
		X-ray	Rh-x	
109	0.52	beta	1.028	
		gamma	0.088, 0.311, 0.636	
		X-ray	Ag-x	
Yttrium				
90	2.67	beta	2.288	3.9
		gamma	2.186	
91	58.8	beta	1.545	3.9
		gamma	1.21	
Gold				
198	2.69	beta	1.371	
		gamma	0.412, 0.676	
199	3.14	beta	0.296, 0.250, 0.462	
		gamma	0.158, 0.208	
		X-ray	Hg-x	

It may be seen that a variety of emission types (i.e., beta particle, alpha particle, gamma rays, X-rays) are available and that the energy levels of the various emissions range from less than 0.1 MeV to over 2.0 MeV. Thus, an advantage may be gained in mixing different emission types and energies.

Insoluble salts of most ions can be made using a suitable counter-ion. For the purposes of the invention a salt is considered to be insoluble if its solubility product constant is lower than about  $1 \times 10^{-5}$ , preferably less than about  $1 \times 10^{-10}$  and most preferably less than  $1 \times 10^{-16}$ .

The radioisotopes in the insoluble salt(s) may be in a cation, an anion or both. The radioisotopes may be in a complex ion optionally comprising one or more other radioisotopes. Suitable radioactive complex ions include  $^{32}\text{PO}_4^{2-}$  and  $^{35}\text{SO}_4^{2-}$ . Two or more different radioisotopes may be present in a single insoluble salt or a mixture of different salts may be used, two or more of which contain different radioisotopes. For example, if  $^{103}\text{Pd}$  and  $^{125}\text{I}$  are the radioisotopes, then they may be present as  $^{103}\text{Pd}(\text{}^{125}\text{I})_2$  or as a mixture of a salt containing palladium-103 with a cold anion (e.g. bromide) and a salt containing iodine-125 and a cold cation (e.g. silver). A source comprising both  $^{103}\text{Pd}$  and  $^{125}\text{I}$  would provide a short intense radioactivity due to the  $^{103}\text{Pd}$  and a longer, lower activity due to the  $^{125}\text{I}$ .

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Two or more radioisotopes may be present as cations or anions in a single salt. Two or more radioisotopes may also be present in the anions or cations of different salts which have the same counterion (e.g.  $^{89}\text{SrPO}_4$  and  $^{51}\text{CrPO}_4$ ). The sources and insoluble salts of the invention

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may also contain 2 or more different radioisotopes of a single element (e.g.  $^{131}\text{I}$  and  $^{125}\text{I}$ ).

5 Additionally, one of the two or more radioisotopes in the salt(s) could be suitable for radio imaging (i.e., gamma imaging). For example, in the salt  $^{111}\text{In}_2^{35}\text{S}_3$ ,  $^{111}\text{In}$  could be used as a radio imaging agent. In an alternative example, the salt  $^{99\text{m}}\text{TcS}$  is well known for its imaging properties but has no therapeutic effect. Combining a  
10 radioactive isotope with  $^{99\text{m}}\text{Tc}$  (e.g. in  $^{99\text{m}}\text{Tc}^{35}\text{S}$ ) would provide an agent with both therapeutic and imaging properties.

Preferably, the different radioisotopes emit  
15 different types or energies of radiation (e.g. alpha, beta, gamma, X-rays etc.), or have different half-lives. Preferred insoluble salts are salts comprising two or more of  $^{125}\text{I}$ ,  $^{103}\text{Pd}$ ,  $^{89}\text{Sr}$ ,  $^{32}\text{P}$  (for example as a phosphate) and  $^{35}\text{S}$  (for example as the sulfate or sulfide). Especially  
20 preferred insoluble salts are  $^{103}\text{Pd}^{(125}\text{I})_2$ ,  $^{103}\text{Pd}^{35}\text{S}$ ,  $^{89}\text{Sr}^{32}\text{PO}_4$  and  $^{89}\text{Sr}^{35}\text{SO}_4$ . Such salts form a further aspect of the invention. Other therapeutically useful isotopes include but are not necessarily limited to the following:  $^{117\text{m}}\text{Sn}$ ,  
25  $^{131}\text{I}$ ,  $^{132}\text{I}$ ,  $^{47}\text{Sc}$ ,  $^{67}\text{Cu}$ ,  $^{186}\text{Re}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{166}\text{Ho}$ ,  $^{212}\text{Bi}$ ,  $^{255}\text{Fm}$ ,  $^{90}\text{Y}$ .

The radioactive sources of the invention may also comprise cold isotopes corresponding to the radioisotopes. Thus the insoluble salts of the sources of the invention  
30 may contain both "hot" (i.e. radioactive) and "cold" (i.e. non-radioactive) isotopes of an element. Dilution of the radioisotopes with corresponding cold isotopes is one method whereby the overall activity of the sources of the invention may be altered or controlled as desired.

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The table below shows the solubility product constants for a number of salts we have identified for use as insoluble salts according to the invention (values taken from The Handbook of Chemistry and Physics, 74th Ed., 1993-1994, section 8, page 49, Lange's Handbook of Chemistry, 14th ed. 1992, section 8, pp 6-11 or other literature). This list is clearly not limiting.

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	Compound	Ksp	Possible Salts
	Bismuth Sulfide	$1.82 \times 10(-99)$	$^{212}\text{Bi}_2^{35}\text{S}_3$ , $^{210}\text{Bi}_2^{35}\text{S}_3$
	Bismuth Iodide	$8.1 \times 10(-19)$	$^{212}\text{Bi}^{125}\text{I}_3$ , $^{212}\text{Bi}^{131}\text{I}_3$ , $^{210}\text{Bi}^{125}\text{I}_3$
	Bismuth Phosphate	$1.3 \times 10(-23)$	$^{212}\text{Bi}^{32}\text{PO}_4$ , $^{210}\text{Bi}^{32}\text{PO}_4$
5	Cadmium Phosphate	$2.5 \times 10(-33)$	$^{109}\text{Cd}_3(^{32}\text{PO}_4)_2$
	Cadmium Sulfide	$8.0 \times 10(-26)$	$^{109}\text{Cd}^{35}\text{S}$
	Chromium Phosphate (green)	$2.4 \times 10(-23)$	$^{51}\text{Cr}^{32}\text{PO}_4 \cdot 4\text{H}_2\text{O}$
	Chromium Phosphate (violet)	$1.0 \times 10(-17)$	$^{51}\text{Cr}^{32}\text{PO}_4 \cdot 4\text{H}_2\text{O}$
	Copper(I) Iodide	$1.27 \times 10(-12)$	$^{64}\text{Cu}^{125}\text{I}$ , $^{67}\text{Cu}^{131}\text{I}$
10	Copper(I) Sulfide	$2.26 \times 10(-48)$	$^{64}\text{Cu}_2^{35}\text{S}$
	Copper(II) Iodate	$7.4 \times 10(-8)$	$^{64}\text{Cu}(^{131}\text{IO}_3)_2$ , $^{67}\text{Cu}(^{125}\text{IO}_3)_2$
	Copper(II) Sulfide	$6.0 \times 10(-37)$	$^{64}\text{Cu}^{35}\text{S}$
	Gold(I) Iodide	$2.0 \times 10(-13)$	$^{198}\text{Au}^{131}\text{I}$ , $^{198}\text{Au}^{125}\text{I}$ , $^{199}\text{Au}^{125}\text{I}$
	Gold(III) Iodide	$1.0 \times 10(-46)$	$^{198}\text{Au}^{131}\text{I}_3$ , $^{198}\text{Au}^{125}\text{I}_3$ , $^{199}\text{Au}^{125}\text{I}_3$
15	Indium Sulfide	$5.7 \times 10(-74)$	$^{111}\text{In}_2^{35}\text{S}_3$
	Lead Sulfide	$3.0 \times 10(-28)$	$^{209}\text{Pb}^{35}\text{S}$ , $^{210}\text{Pb}^{35}\text{S}$ , $^{212}\text{Pb}^{35}\text{S}$
	Lead Sulfate	$1.6 \times 10(-8)$	$^{212}\text{Pb}^{35}\text{SO}_4$
	Lead Hydrogen Phosphate	$1.3 \times 10(-10)$	$^{212}\text{PbH}^{32}\text{PO}_4$
	Lead Phosphate	$8.0 \times 10(-43)$	$^{212}\text{Pb}_3(^{32}\text{PO}_4)_2$
20	Lead Iodide	$7.1 \times 10(-9)$	$^{212}\text{Pb}^{131}\text{I}_2$ , $^{212}\text{Pb}^{125}\text{I}_2$
	Lead Chromate	$2.8 \times 10(-13)$	$^{212}\text{Pb}^{51}\text{CrO}_4$
	Manganese(II) Sulfide	$3.0 \times 10(-14)$	$^{54}\text{Mn}^{35}\text{S}$ , $^{56}\text{Mn}^{35}\text{S}$
	Mercury(I) iodide	$5.33 \times 10(-29)$	$^{197\text{m}}\text{Hg}_2^{125}\text{I}_2$ , $^{197\text{m}}\text{Hg}_2^{131}\text{I}_2$
	Mercury(I) Iodate	$2.0 \times 10(-14)$	$^{197\text{m}}\text{Hg}_2(^{131}\text{IO}_3)_2$ , $^{197\text{m}}\text{Hg}_2(^{125}\text{IO}_3)_2$
25	Mercury(II) iodide	$2.82 \times 10(-29)$	$^{197\text{m}}\text{Hg}^{125}\text{I}_2$ , $^{197\text{m}}\text{Hg}^{131}\text{I}_2$ , $^{197}\text{Hg}^{125}\text{I}_2$
	Palladium(II) sulfide	$2.03 \times 10(-58)$	$^{103}\text{Pd}$ , $^{35}\text{S}$
	Strontium Sulfite	$4.0 \times 10(-8)$	$^{89}\text{Sr}^{35}\text{SO}_3$ , $^{85}\text{Sr}^{35}\text{SO}_3$
	Strontium Sulfate	$3.2 \times 10(-7)$	$^{89}\text{Sr}^{35}\text{SO}_4$ , $^{85}\text{Sr}^{35}\text{SO}_4$
	Strontium Iodate	$3.3 \times 10(-7)$	$^{89}\text{Sr}(^{125}\text{IO}_3)_2$ , $^{89}\text{Sr}(^{131}\text{IO}_3)_2$
30	Strontium Phosphate	$4.0 \times 10(-28)$	$^{89}\text{Sr}_3(^{32}\text{PO}_4)_2$
	Thallium Chromate	$1.0 \times 10(-12)$	$^{201}\text{Tl}_2^{51}\text{CrO}_4$
	Thallium Sulfide	$5.0 \times 10(-21)$	$^{201}\text{Tl}_2^{35}\text{S}$
	Tin(II) sulfide	$1.00 \times 10(-26)$	$^{117\text{m}}\text{Sn}^{35}\text{S}$ , $^{113}\text{Sn}^{35}\text{S}$ , $^{125}\text{Sn}^{35}\text{S}$
	Zinc Sulfide	$2.0 \times 10(-25)$	$^{65}\text{Zn}^{35}\text{S}$
35	Zinc Phosphate	$9.0 \times 10(-33)$	$^{65}\text{Zn}_3(^{32}\text{PO}_4)_2$
	Zinc Iodate	$2.0 \times 10(-8)$	$^{65}\text{Zn}(^{125}\text{IO}_3)_2$ , $^{65}\text{Zn}(^{131}\text{IO}_3)_2$

Other suitable salts include barium sulphate ( $K_{sp} = 1 \times 10^{-7}$ ), palladium oxide, palladium bromide and palladium iodide (D.E. Horner et al., South Eastern regional meeting of American Chemical Society on biological aspects of liquid chromatography, Conf-761002-4, 27 Oct. 1976). In addition to these insoluble radioactive salts, others such as  $^{90}\text{Y}^{32}\text{PO}_4$  may be used. These combinations are useful for therapeutic situations where different dose rates, energies, and types of energies are required (i.e. mixed gamma, beta, or alpha radiation). Also, a combination could afford a therapeutic isotope together with an imaging isotope for improved detection of the device/source after implantation.

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As a further feature of the invention there is provided a method for the preparation of an insoluble radioactive salt suitable for use in brachytherapy, said salt comprising two or more different radioisotopes, said method comprising the steps of

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- a) providing a solution containing a suitable cation,
- b) providing a solution containing a suitable anion,
- c) mixing the solutions of the cation and the anion together such that precipitation of an insoluble radioactive salt occurs.

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As a further feature of the invention there is provided a method for the preparation of a radioactive source for use in brachytherapy comprising one or more insoluble salts wherein the insoluble salt(s) together contain at least two different radioisotopes, the method comprising

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- a) providing a solution containing one or more anions,
- b) providing a solution containing one or more cations,
- 5 the anions and cations of steps a) and b) together comprising at least two different radioisotopes, and
- c) mixing together the solutions of the anion(s) and the cation(s) such that precipitation of one or more
- 10 insoluble salts containing the radioisotopes occurs.

In step c) of either method, a support onto which the insoluble salt(s) may precipitate may optionally be present. Suitable supports for use in the above method

15 include graphite, zeolites, ion exchange resins, ceramics, plastics, polymer matrices or other, preferably porous, materials on which a salt will form. The support may be in the form of a bead, rod, filament or wire. Such supports may then be encapsulated, for example inside a

20 container to form a sealed source, or by plating with a suitable metal, for example silver.

In one embodiment of the methods, a polymer matrix support in particulate form is saturated with a suitable

25 anion or cation by equilibration in a solution thereof, washed if desired, followed by treatment with a solution containing a suitable insoluble-salt-forming cation or anion which results in precipitation of an insoluble salt on the surface of or within pores of the polymer matrix.

30 Such a matrix may itself then be encapsulated, for example within a metal or further polymer or plastics coating if desired.

Together, the cation(s) and the anion(s) will

35 comprise two or more different radioisotopes. The anion(s) and cation(s) may be complex ions. The insoluble



salt(s) may comprise more than two radioisotopes. Depending on the desired level of activity of any radioactive source comprising a radioactive salt prepared according to the method of the invention, the solutions of the anion(s) and/or cation(s) may also comprise "cold" anions or cations corresponding to the anions or cations comprising radioisotopes.

The cation(s) and anion(s) used in the method(s) of the invention are chosen such that together they form an insoluble salt or salts. The counter-ions present in the initial solutions of the anion(s) and cation(s) should preferably be chosen such that they will not form any insoluble salt(s) themselves when the solutions are mixed. The counter-ions therefore suitably remain in solution whilst the insoluble salt(s) precipitates out. The salt(s) can then be filtered off or the solution decanted.

If it is desired to encapsulate the insoluble salt inside a sealed container, the mixing of the two solutions can occur inside the container prior to sealing. For example, an aliquot of a palladium-103 chloride solution ( $^{103}\text{PdCl}_2$ ) may be placed inside an empty metal container followed by an excess of a solution of sulfide ( $^{35}\text{S}$ ), for example as the sodium salt, to form insoluble  $^{103}\text{Pd}^{35}\text{S}$  inside the container, followed by welding shut of the container to form a sealed source or "seed".

Alternatively, the anion used may be hydroxide, for example in the form of an excess of sodium hydroxide solution, to lead to precipitation of palladium-103 hydroxide. Similarly, an excess of silver nitrate solution and a solution of sodium iodide (comprising  $^{125}\text{I}$  or  $^{131}\text{I}$ ) may be used to precipitate a radioactive silver iodide salt.

As a further embodiment of the invention there is provided a method for the preparation of a radioactive source for use in brachytherapy comprising an insoluble radioactive salt, said salt comprising an anion and a cation, the anion and cation together containing two or more different radioisotopes, said method comprising the steps of

- a) adsorbing either the cation or the anion on the surface of a suitable support,
- b) contacting the support with a solution containing the other of the cation or the anion, whereby the insoluble salt forms on the surface of said support, and
- c) optionally removing excess solution.

Suitable supports for use in the above method include graphite, zeolites, ion exchange resins, ceramics, polymer matrices, plastics or other, preferably porous, materials on which a salt will form. The support may be in the form of a bead, rod, filament or wire. Such supports may then be encapsulated, for example inside a container to form a sealed source.

The radioactivity levels of the sources produced using the methods of the invention may be altered or controlled as desired through variation of a number of parameters, including choice of radioisotopes, by dilution of the radioisotopes in the insoluble salts with "cold" isotopes and/or by choice of the size and surface area of the support.

The sources of the invention may be employed in brachytherapy using known methods of implantation or

insertion, as described for example in R. Waksman,  
*Vascular Radiotherapy Monitor*, 1998, 1, 10-18 and  
references therein, and in J.C. Blasko et al,  
*Endocuriether/Hypertherm Oncol*, 3, 131-9, (1987) and H.  
5 Ragde et al, *J Endourol*, 3, 209-18, (1989).

In a further aspect, the invention also provides a  
method of treatment of a condition which is responsive to  
radiation therapy, for example cancer, arthritis or  
10 restenosis, which comprises the temporary or permanent  
placement of a radioactive source comprising one or more  
insoluble salt(s) wherein the insoluble salt(s) together  
contain at least two different radioisotopes, at the site  
to be treated within a patient for a sufficient period of  
15 time to deliver a therapeutically effective dose.  
Preferably, the radioisotopes emit different types or  
energies of radiation selected from the group consisting  
of  $\alpha$ ,  $\beta$ ,  $\gamma$  and X-ray radiation, or have different half-  
lives.

20

Preferably, the methods of treatment of the invention  
are employed for the treatment of prostate cancer or to  
inhibit restenosis at a site within the vascular system of  
a patient which has previously been subjected to PTCA.

25

The following Examples are non-limiting illustrations of the invention. In all the Examples, the ions in the insoluble salts may be replaced by ions comprising an equivalent radioisotope to give radioactive salts. The radioactive ion may be the cation, the anion or both. For example, the strontium used may comprise  $^{90}\text{Sr}$ , the palladium used may comprise  $^{103}\text{Pd}$ , the phosphate used may comprise  $^{32}\text{P}$ , the iodide used may comprise  $^{125}\text{I}$  and the sulfate used may comprise  $^{35}\text{S}$ . A portion of the cations and/or anions used in the Examples of the invention may also be replaced by different ions to give mixtures of more than one insoluble salt.

### Examples

#### Example 1

#### Production of Strontium Phosphate Coated PVA Particles

Twenty milliliters of 0.5M solution of strontium chloride ( $\text{SrCl}_2$ ) was added to one gram of 50 to  $150\mu\text{m}$  polyvinyl alcohol particles (PVA) and rotated for one hour. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

The initial PVA particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected or observed. Optical microscopy was done on the sample in order to determine if coating occurred. The uncoated PVA particles appeared crystalline and fairly transparent.

The coated particles were much more opaque. Inductively coupled plasma analysis of the coated particles determined a strontium concentration of 8.5 mg/gram of PVA.

5 The resulting strontium phosphate coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

10 Example 2

Production of Strontium Sulfate Coated PVA Particles

Twenty milliliters of 0.5M solution of strontium chloride ( $\text{SrCl}_2$ ) was added to one gram of 50 to 150 $\mu\text{m}$  polyvinyl alcohol particles (PVA) and rotated for one  
15 hour. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium sulfate ( $\text{Na}_2\text{SO}_4$ ) solution was  
20 then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

25 The initial PVA particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected or observed. Optical microscopy was done on the sample in order to determine if coating occurred. The uncoated PVA  
30 particles appeared crystalline and fairly transparent. The coated particles were much more opaque.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or  
35 insertion as a brachytherapy source using known planning equipment and software.

Example 3Production of Strontium Carbonate Coated PVA Particles

Twenty milliliters of 0.5M solution of strontium  
5 chloride ( $\text{SrCl}_2$ ) was added to one gram of 50 to  $150\mu\text{m}$   
polyvinyl alcohol particles (PVA) and rotated for one  
hour. The mixture was then placed into a 150-ml beaker  
with a stir bar. The excess solution was decanted off,  
leaving the particles still slightly wet. Thirty-five  
10 milliliters of 0.5M sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) solution was  
then added and the mixture was stirred for fifteen  
minutes. The product was filtered and thoroughly rinsed  
through a 100 mesh metal screen with water and finally  
nanopure water. The particles were then bottled in  
15 nanopure water.

The initial PVA particles were white. The expected  
product of the reaction was also white. Thus, a color  
change within the process was neither expected nor  
observed. Optical microscopy was done on the sample in  
20 order to determine if coating occurred. The uncoated PVA  
particles appeared crystalline and fairly transparent.  
The coated particles were much more opaque.

The resulting coated particles may be placed into a  
conventional seed container, for example a titanium, glass  
25 or polymer container, suitable for implantation or  
insertion as a brachytherapy source using known planning  
equipment and software.

Example 430 Production of Palladium Oxide Coated PVA Particles

Twenty milliliters of a saturated solution of  
palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of 50 to  
150  $\mu\text{m}$  polyvinyl alcohol particles (PVA) and rotated  
35 overnight. The mixture was then placed into a 150-ml  
beaker with a stir bar. The excess solution was decanted

off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium hydroxide (NaOH) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed  
5 through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating overnight, the particles turned from white to dark brown. The addition of sodium hydroxide  
10 then caused the particles to turn a brownish black. The pH of the decanted solution before the addition of sodium hydroxide was 1.04. The pH of the final rinsed product was 10.48. Palladium hydroxide is expected to be a brown/black color, indicating a successful reaction.

15 The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

20

#### Example 5

#### Production of Palladium Iodide Coated PVA Particles (Method 1)

25 Twenty milliliters of a saturated solution of palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of 50 to 150 $\mu\text{m}$  polyvinyl alcohol particles (PVA) and rotated for one hour. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The  
30 mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Fifteen milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for fifteen minutes. The product was  
35 filtered and thoroughly rinsed through a 100 mesh metal

screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to medium brown due to adsorption of palladium ions onto the PVA particles. The addition of potassium iodide then caused the particles to turn a purplish black as expected for formation of palladium iodide. Inductively coupled plasma analysis determined the palladium concentration to be 12.2 mg/gram PVA.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

15

#### Example 6

#### Production of Palladium Bromide Coated PVA Particles

Twenty milliliters of a saturated solution of palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of 50 to 150 $\mu\text{m}$  polyvinyl alcohol particles (PVA) and rotated for one hour. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M potassium bromide (KBr) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to medium brown due to adsorption of palladium ions by the PVA particles. The addition of potassium bromide did not cause any change in color, however, the bromide salt is expected to be similar in color to the



starting palladium solution and hence the lack of color change was as expected.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass  
5 or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### Example 7

#### 10 Production of Palladium Iodide Coated PVA Particles (Method 2)

Twenty milliliters of 2% Iodine ( $I_2$ ) in water was added to one gram of 50 to 150 $\mu$ m polyvinyl alcohol  
15 particles (PVA) and rotated for one hour. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet.  
20 Thirty-five milliliters of a saturated solution of palladium chloride ( $PdCl_2$ ) was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then  
25 bottled in nanopure water.

After rotating for one hour, the particles turned from white to reddish black. The addition of palladium chloride then caused the particles to turn rusty black.

The resulting coated particles may be placed into a  
30 conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 8Production of Strontium Phosphate Coated Cation Exchange Resin

5           Twenty milliliters of 0.5M solution of strontium  
chloride ( $\text{SrCl}_2$ ) was added to one gram of 16 to 40 mesh  
cation exchange resin and rotated for one hour. The resin  
was filtered and thoroughly rinsed through a 100 mesh  
metal screen with water. The mixture was then placed into  
10 a 150-ml beaker with a stir bar. The excess solution was  
decanted off, leaving the resin still slightly wet.  
Thirty-five milliliters of 0.5M sodium hydrogen phosphate  
( $\text{Na}_2\text{HPO}_4$ ) solution was then added and the mixture was  
stirred for fifteen minutes. The product was filtered and  
15 thoroughly rinsed through a 100 mesh metal screen with  
water and finally nanopure water. The resin was then  
bottled in nanopure water.

Both the cation exchange resin and the final product  
were gold. A color change within the process was not  
20 observed nor was precipitation of a thin layer of  $\text{SrPO}_4$   
expected to change the macroscopic color of the ion  
exchange resin. Inductively coupled plasma analysis  
determined the strontium concentration to be 25.7mg/gram  
of cation exchange resin.

25           The resulting coated particles may be placed into a  
conventional seed container, for example a titanium, glass  
or polymer container, suitable for implantation or  
insertion as a brachytherapy source using known planning  
equipment and software.

30

Example 9Production of Strontium Carbonate Coated Cation Exchange Resin

35           Twenty milliliters of 0.5M solution of strontium  
chloride ( $\text{SrCl}_2$ ) was added to one gram of 16 to 40 mesh

cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The resin was then bottled in nanopure water.

Both the cation exchange resin and the final product were gold. A color change within the process was not observed nor was precipitation of a thin layer of  $\text{SrCO}_3$  expected to change the macroscopic color of the ion exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### Example 10

#### Production of Strontium Sulfate Coated Cation Exchange Resin

Twenty milliliters of 0.5M solution of strontium chloride ( $\text{SrCl}_2$ ) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium sulfate ( $\text{Na}_2\text{SO}_4$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly

rinsed through a 100 mesh metal screen with water and finally nanopure water. The resin was then bottled in nanopure water.

Both the cation exchange resin and the final product were gold. A color change within the process was not observed nor was precipitation of a thin layer of  $\text{SrSO}_4$  expected to change the macroscopic color of the ion exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### 15 Example 11

##### Production of Palladium Iodide Coated Cation Exchange Resin (Method 1)

Twenty milliliters of a saturated solution of palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to reddish brown. The addition of potassium iodide then caused the resin to turn black as expected due to formation of the insoluble salt palladium iodide. Inductively coupled plasma analysis determined the

palladium concentration to be 7.4 mg/gram of cation exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### Example 12

#### 10 Production of Palladium Bromide Coated Cation Exchange Resin

Twenty milliliters of a saturated solution of palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M potassium bromide (KBr) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to reddish brown. The addition of potassium bromide then caused the resin to turn deep red as expected due to formation of the insoluble salt palladium bromide.

30 The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

35

Example 13Production of Palladium Iodide Coated Cation Exchange Resin (Method 2)

5           Twenty milliliters of 2% iodine ( $I_2$ ) in water was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker  
10 with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of a saturated solution of palladium chloride ( $PdCl_2$ ) was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly  
15 rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

          After rotating for one hour, the particles turned from gold to red, but the color washed out after the first  
20 rinsing. The addition of palladium chloride then caused the resin to turn reddish brown.

          The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or  
25 insertion as a brachytherapy source using known planning equipment and software.

Example 14Production of Palladium Oxide Coated Cation Exchange Resin

30

          Twenty milliliters of a saturated solution of palladium chloride ( $PdCl_2$ ) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100  
35 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution

was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium hydroxide (NaOH) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly  
5 rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to reddish brown. The addition of sodium  
10 hydroxide then caused the resin to turn reddish black as predicted for the expected palladium oxide precipitate.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or  
15 insertion as a brachytherapy source using known planning equipment and software.

#### Example 15

#### Production of Strontium Phosphate Coated Hydroxyapatite 20 Particles

Twenty milliliters of 0.5M solution of strontium chloride ( $\text{SrCl}_2$ ) was added to one gram of 40 $\mu\text{m}$  hydroxyapatite particles and rotated for one hour. The  
25 particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium  
30 hydrogen phosphate ( $\text{Na}_2\text{HPO}_4$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

35 Both the hydroxyapatite particles and the final product were white. A color change within the process was

neither expected nor observed. Optical microscopy was used to attempt to determine if any coating occurred. A visual difference between the uncoated hydroxyapatite particles and the final product could not be observed at low magnification. Inductively coupled plasma analysis determined the strontium concentration to be 5.8 mg/gram hydroxyapatite.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### Example 16

#### 15 Production of Strontium Carbonate Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M solution of strontium chloride ( $\text{SrCl}_2$ ) was added to one gram of 40 $\mu\text{m}$  hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

The initial hydroxyapatite particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected nor observed. Optical microscopy was used on the sample in an attempt to determine if coating occurred. No change could be determined at low magnification.



The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### Example 17

#### Production of Strontium Sulfate Coated Hydroxyapatite Particles

10

Twenty milliliters of 0.5M solution of strontium chloride ( $\text{SrCl}_2$ ) was added to one gram of  $40\mu\text{m}$  hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium sulfate ( $\text{Na}_2\text{SO}_4$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

Both the particles and the final product were white. A color change within the process was not observed either. Optical microscopy was used in an attempt to determine if any coating occurred. A difference between the uncoated hydroxyapatite particles and the final product could not be determined at low magnification.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

35

Example 18Production of Palladium Oxide Coated Hydroxyapatite  
Particles (Method 1)

5           Twenty milliliters of a saturated solution of  
palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of  $40\mu\text{m}$   
hydroxyapatite particles and rotated for one hour. The  
particles were filtered and thoroughly rinsed through a  
10       500 mesh metal screen with water. The mixture was then  
placed into a 150-ml beaker with a stir bar. The excess  
solution was decanted off, leaving the particles still  
slightly wet. Thirty-five milliliters of 0.5M sodium  
hydroxide ( $\text{NaOH}$ ) solution was then added and the mixture  
15       was stirred for fifteen minutes. The product was filtered  
and thoroughly rinsed through a 500 mesh metal screen with  
water and finally nanopure water. The particles were then  
bottled in nanopure water.

          After rotating for one hour, the particles turned  
from white to brown due to adsorption of the palladium  
20       onto the hydroxyapatite. The addition of sodium hydroxide  
caused the particles to turn dark brown as expected for  
the formation of the nearly black palladium oxide.

          The resulting coated particles may be placed into a  
conventional seed container, for example a titanium, glass  
25       or polymer container, suitable for implantation or  
insertion as a brachytherapy source using known planning  
equipment and software.

Example 19

30       Production of Palladium Iodide Coated Hydroxyapatite  
Particles

          Twenty milliliters of a saturated solution of  
palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of  $40\mu\text{m}$   
35       hydroxyapatite particles and rotated for one hour. The  
particles were filtered and thoroughly rinsed through a

500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to brown. The addition of potassium iodide then caused the particles to turn dark brown as expected for the formation of the nearly black palladium iodide. Inductively coupled plasma analysis determined the palladium concentration to be 14.5 mg/gram hydroxyapatite.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

#### Example 20

#### Production of Palladium Bromide Coated Hydroxyapatite Particles

Twenty milliliters of a saturated solution of palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of  $40\mu\text{m}$  hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Twenty-seven milliliters of 0.5M potassium bromide (KBr) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with

water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to brown. The addition of potassium bromide  
5 did not cause any further change in color as expected for formation of the deep red precipitate of palladium bromide.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass  
10 or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 21  
15 Production of Palladium Oxide Coated Hydroxyapatite  
Particles (Method 2)

Twenty milliliters of a saturated palladium chloride ( $\text{PdCl}_2$ ) was added to one gram of  $40\mu\text{m}$  hydroxyapatite  
20 particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with nanopure water. The particles were then placed in a bottle, covered with aluminium foil and depyrogenated. Depyrogenation involves dry heat treatment  
25 at  $240^\circ\text{C}$  overnight. The dry particles were then bottled dry.

After rotating for one hour, the particles turned from white to brown. A further color change after depyrogenation was not observed.

30 The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

35

Example 22Production of Palladium Iodide Coated PVA Particles  
Repeated with 10% w/w Pd Solution

5           Ten milliliters of a 10% w/w palladium chloride  
solution was added to 0.5 gram of 50 to 150 $\mu$ m polyvinyl  
alcohol particles (PVA) and rotated for over night. The  
particles were filtered and thoroughly rinsed through a  
100 mesh metal screen with water. The mixture was then  
10 placed into a 150-ml beaker with a stir bar. The excess  
solution was decanted off, leaving the particles still  
slightly wet. Seventeen and half milliliters of 0.5M  
potassium iodide (KI) solution was then added and the  
mixture was stirred for twenty-five minutes. The product  
15 was filtered and thoroughly rinsed through a 100 mesh  
metal screen with water and finally nanopure water. The  
particles were then bottled in nanopure water.

After rotating for overnight, the particles turned  
from white to tan. The addition of potassium iodide then  
20 caused the particles to turn a reddish black as expected  
for formation of the insoluble palladium iodide.

The resulting coated particles may be placed into a  
conventional seed container, for example a titanium, glass  
or polymer container, suitable for implantation or  
25 insertion as a brachytherapy source using known planning  
equipment and software.

Example 23Reverse Production of Palladium Iodide Coated  
30 Hydroxyapatite Particles

Twenty milliliters of 0.5M potassium iodide (KI)  
solution was added to one gram of 40 $\mu$ m hydroxyapatite  
particles and rotated for one hour. The particles were  
35 filtered and thoroughly rinsed through a 500 mesh metal  
screen with water. The mixture was then placed into a

150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of a saturated palladium chloride solution ( $\text{PdCl}_2$ ) was then added and the mixture was

5 stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles remained

10 white. The addition of palladium chloride caused the particles to turn tan as would be expected for the formation of a small coating of the nearly black palladium iodide.

The resulting coated particles may be placed into a

15 conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

20 Example 24

Reverse Production of Silver Iodide Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M potassium iodide (KI)

25 solution was added to one gram of  $40\mu\text{m}$  hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was

30 decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M silver nitrate ( $\text{AgNO}_3$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and

35 finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles remained white. The addition of silver nitrate caused the particles to turn yellowish green as expected for the formation of silver iodide on the particle surface.

5       The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

10

#### Example 25

#### Reverse Production of Strontium Phosphate Coated Hydroxyapatite Particles

15       Twenty milliliters of 0.5M sodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4$ ) solution was added to one gram of  $40\mu\text{m}$  hydroxyapatite particles and rotated for over night. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then  
20 placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M strontium chloride ( $\text{SrCl}_2$ ) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered  
25 and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

Both the hydroxyapatite particles and the final product were white. A color change within the process was  
30 neither observed nor expected.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning  
35 equipment and software.

Example 26Production of Palladium Iodide-Silver Coated PVA Particles

One gram of palladium iodide coated PVA particles was  
5 pre-soaked in 8mM tin chloride ( $\text{SnCl}_2$ ) solution for one  
hour. The treated particles were then rotated in twenty  
milliliters of 0.5M silver nitrate ( $\text{AgNO}_3$ ) solution for  
three hours. The mixture was transferred to a 250  
milliliter beaker and stirred. Fifty milliliters of 7%  
10 sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) solution was placed into a 150ml  
beaker and stirred. Fifty milliliters of a solution  
containing 0.72% of both silver nitrate ( $\text{AgNO}_3$ ) and  
ammonium nitrate ( $\text{NH}_4\text{NO}_3$ ); 0.66% tungstosilicic acid  
(TSA); and 1.31% formaldehyde was prepared. This solution  
15 was quickly added to the sodium carbonate solution. The  
mixture was then immediately added to the stirring  
particles. After fifteen minutes, 100 milliliters of 5%  
acetic acid was added. The particles were then thoroughly  
rinsed through a 100 mesh metal filter with water and then  
20 nanopure water. The particles were bottled in nanopure  
water.

No color change was observed until the mixture of the  
two solutions was added to the stirring light black  
particles (coated with  $\text{PdI}_2$ ). Within five to ten minutes  
25 after this point, the stirring solution turned from crème  
brown to tan to grey and finally to black. The rinsed  
particles were black as expected for electrodeless  
deposition of metallic silver on top of the palladium  
iodide layer already on the particle surface. The  
30 resulting silver metal coated, palladium iodide containing  
PVA particles are suitable for use as brachytherapy  
sources for implantation or insertion in various tumours,  
in joints for relief of arthritis pain, and for prevention  
of restenosis. Alternatively the resulting coated  
35 particles may be placed into a conventional seed  
container, for example a titanium, glass or polymer



container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

5 Example 27

Production of Palladium Iodide-Silver Coated Ion Exchange Particles

One gram of palladium iodide coated ion exchange resin  
10 was pre-soaked in 8mM tin chloride ( $\text{SnCl}_2$ ) solution for one hour. The treated resin was then rotated in twenty milliliters of 0.5M silver nitrate ( $\text{AgNO}_3$ ) solution for three hours. The mixture was transferred to a 250 milliliter beaker and stirred. Fifty milliliters of 7%  
15 sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) solution was placed into a 150ml beaker and stirred. Fifty milliliters of a solution containing 0.72% of both silver nitrate ( $\text{AgNO}_3$ ) and ammonium nitrate ( $\text{NH}_4\text{NO}_3$ ); 0.66% tungstosilicic acid (TSA); and 1.31% formaldehyde was prepared. This solution  
20 was quickly added to the sodium carbonate solution. The mixture was then immediately added to the stirring resin. After fifteen minutes, 100 milliliters of 5% acetic acid was added. The resin was then thoroughly rinsed through a 100 mesh metal filter with water and then nanopure water.  
25 The resin was bottled in nanopure water.

No color change was observed until the mixture of the two solutions was added to the stirring black resin (coated with  $\text{PdI}_2$ ). Within five to ten minutes after this point, the stirring solution turned from crème brown to  
30 tan to grey and finally to black as the silver metal was electrodelessly plated onto the ion exchange beads already coated with palladium iodide. The resulting silver metal coated, palladium iodide containing ion-exchange resin particles are suitable for use as brachytherapy sources  
35 for implantation or insertion in various tumours, in joints for relief of arthritis pain, and for prevention of

restenosis. Alternatively the resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source  
5 using known planning equipment and software.

Example 28

Deposition of Palladium Iodide on a Variety of Substrates

10 The method cited in Example 5 applied to a variety of substrates as listed here:

- a. Nylon beads
- b. Molecular sieves (zeolites)
- 15 c. Clays (magnesium and aluminium silicates)
- d. Glass beads
- e. Anion exchange resins

The basic procedure was to first rotate the particles in a  
20 solution of  $\text{PdCl}_2$  and then expose them to a solution of KI. The order was reversed for the anion exchange resin. All the samples showed some degree of coating except the glass beads. In general, exposure to the palladium solution caused a marked darkening of the particle surface  
25 indicating the binding of palladium ions. Subsequent exposure to KI produced a black coloured particle, indicating precipitation of  $\text{PdI}_2$  onto the particle surface.

30 Example 29

Preparation of a titanium seed suitable for brachytherapy using  $^{103}\text{Pd}^{125}\text{I}_2$  precipitated onto hydroxyapatite as the radioactive source

35 Twenty milliliters of a saturated solution of radioactive (103)palladium chloride ( $^{103}\text{PdCl}_2$ ) is added to

one gram of 0.5 mm hydroxyapatite particles and rotated for one hour. The particles are filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture is then placed into a 150-ml beaker with a stir bar. The excess solution is decanted off, leaving the particles still slightly wet. Thirty-five milliliters of a 0.5 M solution of radioactive potassium (125) iodide ( $K^{125}I$ ) is then added and the mixture is stirred for fifteen minutes. The product is filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles are then bottled in nanopure water.

After rotating in the (103) palladium solution for one hour, the particles turn from white to brown. The addition of potassium (125) iodide causes the particles to turn dark brown as expected for the formation of the nearly black palladium iodide.

The resulting particles are placed into a conventional titanium seed container which has been plasma arc welded at one end. By analogy with the conventional seeds prepared using  $^{125}I$  adsorbed onto ion exchange resin beads, these 0.5 mm particles are placed 4 to a container. The container top is then crimped and welded shut to make the resulting seed suitable for use in brachytherapy.

Levels of radioactivity are controlled through dilution of the radioactive ions with "cold" ions for complete coating of the beads. Thus the levels of radioactivity may be adjusted from as low as 0.1 millicurie/seed to over 10 millicuries/seed although generally, 0.4 to 2 millicuries/seed is desired for prostate cancer treatment. Higher levels of activity/seed may be achieved by using much smaller hydroxyapatite beads with increased surface area and hence greater amounts of  $^{103}Pd^{125}I_2$  coating. Such seeds may be suitable for prevention or treatment of restenosis.

Claims

1. A radioactive source suitable for use in brachytherapy comprising one or more insoluble salts  
5 wherein the insoluble salt contains, or the insoluble salts together contain, at least two different radioisotopes.
2. A radioactive source as claimed in claim 1 wherein a  
10 single insoluble salt comprising at least two different radioisotopes is used.
3. A radioactive source as claimed in claim 2 wherein an anion and a cation of the salt each comprise at least one  
15 radioisotope.
4. A radioactive source as claimed in any of claims 1 to 3 wherein the radioisotopes emit different types or energies of radiation or have different half-lives.  
20
5. A radioactive source as claimed in any of claims 1 to 4 wherein the insoluble salt includes  $^{125}\text{I}$ ,  $^{103}\text{Pd}$ ,  $^{89}\text{Sr}$ ,  $^{35}\text{S}$  or  $^{32}\text{P}$ .
- 25 6. A radioactive source as claimed in any of claims 1 to 5 wherein the insoluble salt is  $^{103}\text{Pd}(^{125}\text{I})_2$ ,  $^{103}\text{Pd}^{35}\text{S}$ ,  $^{89}\text{Sr}^{32}\text{PO}_4$  or  $^{89}\text{Sr}^{35}\text{SO}_4$ .
7. A radioactive source as claimed in any of claims 1 to  
30 6 where one of the radioisotopes possesses at least one gamma emission with an energy suitable for external imaging outside the human body.
8. A radioactive source as claimed in any of claims 1 to  
35 7 further comprising a suitable non-radioactive support material for the insoluble salt(s).

9. A radioactive source as claimed in any of claims 1 to 8 when the source is sealed within a biocompatible container.

5

10. An insoluble salt suitable for use in brachytherapy which comprises two or more different radioisotopes, with the proviso that the salt is not a pyrophosphate salt.

10 11. An insoluble salt as claimed in claim 10 which is  $^{103}\text{Pd}(^{125}\text{I})_2$ ,  $^{89}\text{Sr}^{32}\text{PO}_4$ ,  $^{89}\text{Sr}^{35}\text{SO}_4$  or  $^{103}\text{Pd}^{35}\text{S}$ .

12. A radioactive composition which comprises an insoluble salt as claimed in any of claims 10 or 11  
15 together with a suitable non-radioactive support.

13. A method for the preparation of an insoluble salt as claimed in claim 10 or claim 11 which comprises:

- 20 (a) providing a solution of a suitable radioactive salt-forming anion,  
(b) providing a solution of a corresponding radioactive salt-forming cation,  
(c) mixing the solutions of the anion and cation together so that precipitation of the insoluble  
25 salt occurs.

14. A method for the preparation of a composition as claimed in claim 12 which comprises carrying out step (c) of claim 13 in the presence of a suitable non-radioactive  
30 support.

15. A method of treatment of a condition which is responsive to radiation therapy, which comprises the temporary or permanent placement of a radioactive source  
35 comprising one or more insoluble salts, wherein the insoluble salt contains, or the insoluble salts together

contain, at least two different radioisotopes, at the site to be treated within a patient for a sufficient period of time to deliver a therapeutically effective dose, and with the proviso that such salts are not pyrophosphate salts.

5

16. A method as claimed in claim 15 wherein the radioisotopes emit different types or energies of radiation or have different half-lives.

10 17. A method as claimed in any of claims 15 or claim 16 for the treatment of cancer, arthritis or restenosis.

18. A method as claimed in any of claims 15 to 17 for the treatment of prostate cancer or to inhibit restenosis.

## INTERNATIONAL SEARCH REPORT

Internat Application No  
PCT/GB 99/03774A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K51/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US WISNER E R ET AL: "Contrast-enhancement properties of irradiated normal lymph nodes: initial experience with interstitially delivered iodinated nanoparticles." retrieved from STN Database accession no. 1998221847 XP002134177 abstract & ACADEMIC RADIOLOGY, (1998 APR) 5 SUPPL 1 S180-2;DISCUSSION S183-4. ,  -/-	1-18

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- "&" document member of the same patent family

Date of the actual completion of the international search

28 March 2000

Date of mailing of the international search report

10/04/2000

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## INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/GB 99/03774

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	<p>WO 99 33766 A (COMMISSARIAT ENERGIE ATOMIQUE ;LACOUT JEAN LOUIS (FR); CARPENA JOE) 8 July 1999 (1999-07-08) page 7, line 7 - line 27; claims page 9, line 28 -page 10, line 28; claims 1,4,15</p>	1
A	<p>US 4 505 888 A (MOORE HERBERT ET AL) 19 March 1985 (1985-03-19) claims</p>	
X	<p>WO 97 19706 A (IBT TECHNOLOGY PARTNERS ;RUSSELL JOHN L JR (US); CONIGLIONE ROY (U) 5 June 1997 (1997-06-05) page 18, line 12 - line 32; claims</p>	1-18
Y	<p>WO 97 01304 A (MALLINCKRODT MEDICAL INC) 16 January 1997 (1997-01-16)</p>	1-18
X	<p>claims</p>	1
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 03774

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 15-18  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/03774

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